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THE COUNCIL FOR TOBACCO RESEARCH-U.S.A.

110 EAST 59TH STREET
NEW YORK, N.Y. 10022
(212) 421-8985

JUN 23 1975

Application for Research Grant
(Use extra pages as needed)

Date: June 17, 1975

1. Principal Investigator (give title and degrees):

Professor Lars Friberg, M.D., Co-investigator Docent Rune Cederlöf
Ph.D.

2. Institution & address:

The Karolinska Institute
Department of Environmental Hygiene
S-104 01 Stockholm, Sweden

3. Department(s) where research will be done or collaboration provided:

Department of Environmental Hygiene

4. Short title of study: Causes of death in relation to smoking habits and other behavioral and environmental factors. A study on the Swedish twin registry.

5. Proposed starting date: February 1, 1975

? 1976?

6. Estimated time to complete: 3 years

7. Brief description of specific research aims: The Swedish twin registry, covering a total of about 11,000 twin pairs of the same sex, has been in operation since 1961. The main line of research has been to study gross and cause specific mortality against the background of smoking habits, alcohol problems and other smoking associated variables in twins. Results were reported in 1973 in the Archives of Environmental Health (enclosure 1). The report covered an 11 year study on 9,000 twin pairs, of same sex born 1901 to 1925.

In addition to intramural funds from the Karolinska Institute and the Swedish National Environment Protection Board, during the years 1971 to 1975 the investigations were supported by a grant from the American Medical Association Education and Research Foundation. As the last mentioned agency is no longer in operation, the present application asks for financial support to continue the mortality follow-up study for the years 1976 through 1978.

Further details appear in enclosure 2.

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8. Brief statement of working hypothesis:

Smokers and nonsmokers can be assumed to differ in many other respects than smoking. These differences may be partly genetic and partly environmental. A direct comparison of the mortality outcome between smokers and nonsmokers in general cannot be made without due consideration to these factors. Research on smoking discordant twin pairs enhances the group comparability. Monozygotic twins offer complete genetic control, identity as to age and sex, and assumingly a far greater environmental similarity than smokers and nonsmokers in general. Fraternal twins constitute an ideal group for comparison.

Two extreme major hypotheses can be contrasted and put to test in the twin research design, namely

1. The observed statistical relationship between smoking and disease parameters is of a causal nature.
2. The observed statistical relationship between smoking and disease parameters is due to genetic and/or environmental factors correlated to smoking.

9. Details of experimental design and procedures (append extra pages as necessary)

See enclosure 2

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10. Space and facilities available (when elsewhere than item 2 indicates, state location):

Ordinary office space and equipment

Computers: Nova 1220

Access to IBM 360/75, belonging to the University
of Stockholm

11. Additional facilities required:

None

12. Biographical sketches of investigator(s) and other professional personnel (append):

Known to the CTR

13. Publications: (five most recent and pertinent of investigator(s); append list, and provide reprints if available).

See enclosure 3

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14. First year budget:

A. Salaries (give names or state "to be recruited")

Professional (give % time of investigator(s)
even if no salary requested)

Present salary through Dec. 1975

Research ass. Ulla Lorich B.A.	100	13,857
Clerical ass.		4,000
Soc. security 33%		5,893
Expected annual increase 10%		2,375

1 \$ = 3.89 Skr

Technical

% time

Amount

Sub-Total for A

26,125

ok
for

B. Consumable supplies (by major categories)

Sub-Total for B

C. Other expenses (itemize)

Computer work 2,500

Sub-Total for C

2,500

Running Total of A + B + C

28,625

D. Permanent equipment (itemize)

Sub-Total for D

4,294

Total request

32,919

E. Indirect costs (15% of A+B+C)

15. Estimated future requirements:

	Salaries	Consumable Suppl.	Other Expenses	Permanent Equip.	Indirect Costs	Total
Year 2	28,737		2,500		4,686	35,923
Year 3	31,611		2,500		5,117	39,228

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5.

16. Other sources of financial support:

List financial support from all sources, including own institution, for this and related research projects.

CURRENTLY ACTIVE

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Causes of death in relation to smoking habits and other behavioral and environmental factors. A study on the Swedish twin registry	The American Medical Association Education and Research Foundation No 353	8 27,214	Feb. 1 1975-Jan. 31 1976

PENDING OR PLANNED

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Maintenance of the twin registries	National Swedish Environment Protection Board	8 18,300	July 1 1975-June 31 1976
Epidemiological studies on the new Swedish twin registry	The Council for Tobacco Research	43,923	July 1 1975-June 31 1977

It is understood that the investigator and institutional officers in applying for a grant have read and accepted the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Principal investigator

Typed Name Lars Friberg
Signature Lars Friberg Date 25 06 17

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Responsible officer of institution

Typed Name Margareta Almling
Title Head of Administration
Signature M. Almling Date 25 06 17
Telephone 08 34 05 60 1123
Area Code 08 Number 34 05 60 Extension 1123

Checks payable to

The Karolinska Institute

Mailing address for checks

The Karolinska Institute
S-104 01 Stockholm, Sweden

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General outline of proposed research

The Twin Research Program at the Department of Environmental Hygiene of the Karolinska Institute as well as of the Swedish National Environment Protection Board was started in 1959 by the compilation of a twin registry covering all twin pairs of the same sex, born between 1886 and 1925 and still living in the country at the time of compilation (about 11 000 complete pairs). The main reason for setting up the registry was to find twin pairs with different environmental exposures, such as different smoking habits. The aim was to follow such twin pairs for a long period of time and to analyze some disease symptoms and signs as well as subsequent mortality in relation to e.g. different types and amounts of smoking. The research has been concentrated upon smoking but a large variety of other items has been studied at the same time, partly because of the confounding correlation of these items to the smoking habit, and partly because of interest in their own effects. The registry has also been used for some special clinical investigations, relating mostly to the effect of smoking and other behavioral factors in connection with ischemic heart disease.

The results from the registry have been published in medical journals and have also appeared as monographs (a list of publications is attached as enclosure 3). A comprehensive report is now being prepared, partly as a guide line for researchers who want to embark on twin studies and partly as a summary of the highlights of results hitherto obtained within the frame of the Swedish research. This report will appear in 1976 and is financially supported by the CTR.

Of main interest for the present application are the results from the twin registry in regard to mortality. An 11-year follow-up study was published in 1973 (enclosure 1) and updated reports (enclosure 1, 4, 5) have subse-

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quently been submitted to the American Medical Association Education and Research Foundation, which provided the funding. As these reports provide details in regard to methodology and data validity only a very brief summary of the main results will be given here.

The analysis was approached in two ways, first as a "conventional" epidemiological study on the twins without any regard paid to their pairing. The results showed the usual relationship between smoking and gross mortality, displaying relative risk of about 2-2.5 for male smokers of 10+ cigarettes a day; the corresponding figure for women was about 2.

The second approach was an analysis of the smoking discordant twin pairs. It was shown that among 706 male dizygotic smoking discordant pairs 55 deaths or "first deaths" occurred in a high smoking group in comparison to 31 such deaths in a low smoking group, i.e. a relative risk of 1.8. Among 246 corresponding monozygotic male pairs, the numbers were 18 versus 18, giving a ratio of unity. About the same dissimilarity between the dizygotic and monozygotic group was also seen in females. Unpublished data from the extended follow-up through June 1974 (enclosure 5) showed 71 deaths in a high smoking group and 46 deaths in a low smoking group among dizygotes, while the corresponding figures in the monozygotic group were 23 versus 22, still counted as deaths or "first deaths". The numbers become very small and show a considerable statistical variation if broken down by age and by varying degrees of smoking discordance. The hypermortality in the dizygotic groups was mainly due to coronary heart disease, lung cancer, suicides and accidents.

The 1973 publication also considered alcohol habits, reflected as a registration in a nationwide registry comprising people who had been in conflict with the society due to misdemeanors in connection with alcohol abuse. It was found that among the nonsmokers in the

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study 8-10 percent were so registered as against 25-30 percent among smokers of 10+ cigarettes a day. The mortality among the registered subjects showed up to be significantly higher than the nonregistered already in the nonsmoking group, i.e. 2.7 versus 4.3 percent among males born 1911-1925, and 10.2 versus 17.3 percent among males born 1901-1910. In 4 och 6 comparisons within smoking groups the mortality was higher among the registered. These findings directly point to the fact that the smoking effect cannot be evaluated unless drinking habits are controlled.

It has not yet been possible to examine to any great extent the confounding effect of social and habitual variables other than drinking in the rather limited series of discordant twins, even though the importance of such factors has been demonstrated on a non-pair basis in the total sample (enclosures 1, 4, 5).

It is considered of very great importance, however, that the mortality study be continued until such numbers of death are reached that will allow closer analysis. It shall be pointed out that the number of deaths can be expected to increase considerably during the coming 3 years, depending on the age structure of the twin series. Up to June 1974 2 959 deaths have occurred and another 1 990 deaths are expected to occur up to June 1978. Among those born 1901-1925, 1 393 deaths occurred up to June 1974 and another 1 026 deaths are expected to occur up to June 1978.

This project has been funded during 1971 to 1975 by a 5 year grant from the American Medical Association Education and Research Foundation, as well as by intramural funds from the Karolinska Institute and the Swedish National Environment Protection Board. As the AMA agency has now terminated its operation we are hereby requesting corresponding financial support from the Council for Tobacco Research - USA, Inc. for the time period 1976-1978.

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STUDIES ON THE SWEDISH TWIN REGISTRY

Enclosure 3

Year	No	Author	Title and publication
1959	64	Friberg, L Kaij, L Dencker, S J Jonsson, E	Smoking Habits of Monozygotic and Dizygotic Twins. Brit. Med. J. 1959, I:1090-1092
1961	103	Cederlöf, R Friberg, L Jonsson, E Kaij, L	Studies on Similarity Diagnosis in Twins with the Aid of Mailed Questionnaires. Acta Genet. 11:338-362, 1961.
1963	134	Cederlöf, R Friberg, L Jonsson, E Kaij, L	Morbidity among Monozygotic Twins with Reference to Smoking Habits and Place of Residence. Preprint, Stockholm 1963.
1964	145	Cederlöf, R	Tvillingregistret. Preliminärt meddelande Nord. Hyg. Tidskr. 45:63-70, 1964.
	146	Cederlöf, R Friberg, L Jonsson, E Kaij, L	Sjuklighet hos enäggstvillingar med hän-syn till rökanor och bostadsort. Nord. Hyg. Tidskr. 45:71-75, 1964.
1965	157	Cederlöf, R Friberg, L Jonsson, E Kaij, L	Morbidity among Monozygotic Twins. Arch. Environ. Health 10:346-350, 1965.
1966	170	Lundman, T	Smoking in Relation to Coronary Heart Disease and Lung Function in Twins. Acta Med. Scan. 180: Suppl. 455, 1966. Akad. avhandling.
	184	Cederlöf, R	The Twin Method in Epidemiological Studies on Chronic Disease. Stockholm 1966, Akad. avhandling.
1967	186	Cederlöf, R Friberg, L Jonsson, E Kaij, L	Respiratory Symptoms and "Angina Pectoris" in Twins with reference to Smoking Habits An Epidemiological Study with Mailed Questionnaire. Arch. Environ. Health 13:726-737, 1966
	187	Cederlöf, R Jonsson, E Lundman, T	On the Validity of Mailed Questionnaires in Diagnosing "Angina Pectoris" and "Bronchitis". Arch. Environ. Health 13:738-742, 1966.
	188	Cederlöf, R	Urban Factor and Prevalence of Respirator Symptoms and "Angina Pectoris". A Study of 9,168 Twin-Pairs with the Aid of Mailed Questionnaires. Arch. Environ. Health 13:743-748, 1966.

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Year	No	Author	Title and publication
1967	190	Cederlöf, R Friberg, L Jonsson, E	Hereditary Factors and "Angina Pectoris". A Study on 5,877 Twin-Pairs with the Aid of Mailed Questionnaires. Arch. Environ. Health <u>14</u> :397-400, 1967.
	191	Cederlöf, R Edfors, M-L Friberg, L Jonsson, E	Hereditary Factors, "Spontaneous Cough" and "Smoker's Cough". A Study on 7,800 Twin-Pairs with the Aid of Mailed Questionnaires. Arch. Environ. Health <u>14</u> :401-406, 1967.
1968	215	Cederlöf, R Friberg, L	Tobaksrökning och hälsa. Resultat från epidemiologiska tvillingundersökningar. Läkartidningen <u>65</u> :2727-2734, 1968.
	227	Jonsson, E Nilsson, T	Alkoholkonsumtion hos monozygota och dizygota tvillingpar. Nord. Hyg. Tidskr. <u>49</u> :21-25, 1968.
1969	246	Cederlöf, R Friberg, L Hrubec, Z	Cardiovascular and Respiratory Symptoms in Relation to Tobacco Smoking. A Study on American Twins. Arch. Environ. Health <u>18</u> :934-940, 1969.
	249	Liljefors, I Piscator, M Risinger, C	Exercise Proteinuria in Monozygotic and Dizygotic Twins. Medicine and Sport <u>3</u> :333-339, 1969.
1970	266	Liljefors, I	Coronary Heart Disease in Male Twins. Hereditary and environmental factors in concordant and discordant pairs. Stockholm 1970. Akad. avhandling.
	277	Friberg, L Cederlöf, R Lundman, T Olsson, H	Mortality in Smoking Discordant Monozygotic and Dizygotic Twins. A Study on the Swedish Twin Registry. Arch. Environ. Health <u>21</u> :508-513, 1970.
1971	281	Cederlöf, R Floderus, B Friberg, L	Cancer in MZ and DZ Twins. Acta Genet. Med. Gemellol. <u>19</u> :69-74, 1970.
	282	Cederlöf, R Floderus, B Friberg, L	The Swedish Twin Registry. Past and future use. Acta Genet. Med. Gemello. <u>19</u> :351-354 1970.
	284	Cederlöf, R Epstein, F H Friberg, L Hrubec, Z Redford, E P	Twin Registries in the Study of Chronic Disease with Particular Reference to the Relation of Smoking to Cardiovascular and Pulmonary Diseases. Repl on and Internat. Symp. in San Juan, Puerto Rico, 1-4 Dec. 1969. Acta. Med. Scan. Suppl. 523, 1971.
	286	Lundman, T Liljefors, I Cederlöf, R Friberg, L	The Validity of the Questionnaire Diagnosis "Angina Pectoris". Arch. Environ. Health <u>22</u> :597-599, 1971.

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Year	No	Author	Title and publication
1971	292	Edfors-Luba, M-L	Allergy in 7,000 Twin Pairs. Acta Aller. <u>26</u> :249-285, 1971.
	294	Cederlöf, R Kaij, L	The Effect of Childbearing on Bodyweight. A Twin Control Study. Acta Psychiat. Scand. <u>46</u> : Suppl. 219:47-49, 1970.
	295	Cederlöf, R	The Use of Twin Studies in CNSLD. Ur Bronchitis III. Proc. of the 3:rd internat. Symposium on Bronchitis at Gronningen, 23-26 Sept. 1969, pp 120-127.
1972	324	Camner, P Philipson, K Friberg, L	Tracheobronchial Clearance in Twins. Arch. Environ. Health <u>24</u> :82-87, 1972.
	333	Camner, P Philipson, K	Tracheobronchial Clearance in Smoking-Discordant Twins, Arch. Environ. Health <u>25</u> :60-63, 1972.
	339	Helander, E	Om frekvensen av fylleristraff, särskilt hos tvillingar. Socialmedicinsk tidsskr. <u>49</u> :555-561, 1972.
1973	369	Hrubec, Z Cederlöf, R Friberg, L Horton, R Ozolins, G	Respiratory Symptoms in Twins. Arch. Environ. Health <u>27</u> :189-195, 1973.
	390	Friberg, L Cederlöf, R Lorich, U Lundman, T de Faire, U	Mortality in Twins in Relation to Smoking Habits and Alcohol Problems. Arch. Environ. Health <u>27</u> :294-304, 1973.
1974		Myrhed, M	Alcohol Consumption in Relation to Factors Associated with Ischemic Heart Disease. Acta Medica Scand. Suppl. 567, Akad. avh.
		Floderus, B	Psycho-social Factors in Relation to Coronary Heart Disease and Associated Risk Factors. Nord. Hyg. Tidskr. Suppl. 6, Akad. avhandling.
		de Faire, U	Ischemic Heart Disease in Death Discordant Twins. Acta Medica Scand. Suppl. 568. Akad. avhandling.
1975		Medlund, P Cederlöf, R Floderus, B Friberg, L Sörensen, S	The New Swedish Twin Registry. A registry of births for 110,000 twins and of addresses for 80,000 twins born 1926-27 plus basedata on environmental medicine factors for 32,000 twins (13,700 complete same-sexed pairs) born 1926-1958.

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